

```
%^STN;highlightOn= ***;highlightOff=*** ;
Trying 3106016892...Open
```

```
Welcome to STN International!  Enter x:x
LOGINID:ssspta1642jxh
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2
```

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

|      |    |        |  |
|------|----|--------|--|
| NEWS | 1  |        | Web Page URLs for STN Seminar Schedule - N. America                      |
| NEWS | 2  | Dec 17 | The CA Lexicon available in the CAPLUS and CA files                      |
| NEWS | 3  | Feb 06 | Engineering Information Encompass files have new names                   |
| NEWS | 4  | Feb 16 | TOXLINE no longer being updated  |
| NEWS | 5  | Apr 23 | Search Derwent WPINDEX by chemical structure                             |
| NEWS | 6  | Apr 23 | PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA                      |
| NEWS | 7  | May 07 | DGENE Reload   |
| NEWS | 8  | Jun 20 | Published patent applications (A1) are now in USPATFULL                  |
| NEWS | 9  | JUL 13 | New SDI alert frequency now available in Derwent's<br>DWPI and DPCI      |
| NEWS | 10 | Aug 23 | In-process records and more frequent updates now in<br>MEDLINE           |
| NEWS | 11 | Aug 23 | PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA                       |
| NEWS | 12 | Aug 23 | Adis Newsletters (ADISNEWS) now available on STN                         |
| NEWS | 13 | Sep 17 | IMSworld Pharmaceutical Company Directory name change<br>to PHARMASEARCH |

```
NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
                CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
                AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS world wide web Site (general information)
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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 16:34:42 ON 21 SEP 2001

```
=> file registry/cn
'REGISTRY/CN' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'HOME'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
```

|                      |            |         |
|----------------------|------------|---------|
| => file registry     |            |         |
| COST IN U.S. DOLLARS | SINCE FILE | TOTAL   |
|                      | ENTRY      | SESSION |
| FULL ESTIMATED COST  | 0.15       | 0.15    |

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
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```
STRUCTURE FILE UPDATES: 20 SEP 2001 HIGHEST RN 357913-38-3
DICTIONARY FILE UPDATES: 20 SEP 2001 HIGHEST RN 357913-38-3
```

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT  
for details.

=> e apb/cn

|     |       |  |
|-----|-------|--|
| E1  | 1     | APAXIFYLLINE/CN  |
| E2  | 1     | APAZONE/CN   |
| E3  | 2 --> | APB/CN   |
| E4  | 1     | APB (CORROSION INHIBITOR)/CN   |
| E5  | 1     | APB-BMI/CN   |
| E6  | 1     | APBB/CN  |
| E7  | 1     | APBE (PASTEURELLA MULTOCIDA STRAIN IL1403 CLONE PM70 GENE AP<br>BE)/CN |
| E8  | 6     | APC/CN   |
| E9  | 1     | APC (ACCELERATOR)/CN   |
| E10 | 1     | APC (CAENORHABDITIS ELEGANS GENE EMB-27 SUBUNIT 6)/CN                  |
| E11 | 1     | APC (PESTICIDE)/CN   |
| E12 | 1     | APC (PHARMACEUTICAL)/CN  |

=> s e3

L1 2 APB/CN

=> d l1 1-2

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2001 ACS  
RN 139689-20-6 REGISTRY  
CN 1H-3-Benzazepine-7,8-diol, 6-bromo-2,3,4,5-tetrahydro-1-phenyl-3-(2-  
propenyl)-, (1R)- (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN 1H-3-Benzazepine-7,8-diol, 6-bromo-2,3,4,5-tetrahydro-1-phenyl-3-(2-  
propenyl)-, (R)-  
OTHER NAMES:  
CN \*\*\*APB\*\*\*  
FS STEREOSEARCH  
MF C19 H20 Br N O2  
CI COM  
SR CA  
LC STN Files: BEILSTEIN\*, CA, CAPLUS, TOXLIT  
(\*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).

/ Structure 1 in file .gra /

15 REFERENCES IN FILE CA (1967 TO DATE)  
15 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2001 ACS  
RN 12765-00-3 REGISTRY  
CN APB (corrosion inhibitor) (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN \*\*\*APB\*\*\*  
MF Unspecified  
CI MAN  
LC STN Files: CA, CAPLUS, TOXLIT

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
7 REFERENCES IN FILE CA (1967 TO DATE)  
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> e apb domain/cn

|     |       |  |
|-----|-------|--|
| E1  | 2     | APB/CN   |
| E2  | 1     | APB (CORROSION INHIBITOR)/CN   |
| E3  | 0 --> | APB DOMAIN/CN  |
| E4  | 1     | APB-BMI/CN   |
| E5  | 1     | APBB/CN  |
| E6  | 1     | APBE (PASTEURELLA MULTOCIDA STRAIN IL1403 CLONE PM70 GENE AP<br>BE)/CN |
| E7  | 6     | APC/CN   |
| E8  | 1     | APC (ACCELERATOR)/CN   |
| E9  | 1     | APC (CAENORHABDITIS ELEGANS GENE EMB-27 SUBUNIT 6)/CN                  |
| E10 | 1     | APC (PESTICIDE)/CN   |
| E11 | 1     | APC (PHARMACEUTICAL)/CN  |

E12 1 APC 1/CN

=> log off  
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF  
LOGOFF? (Y)/N/HOLD:y

\* \* \* \* \*

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\* \* \* \* \*

STN INTERNATIONAL LOGOFF AT 16:36:32 ON 21 SEP 2001

Trying 3106016892...Open

Welcome to STN International! Enter x:x  
LOGINID:ssspta1642jxh  
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|---------|--------|--|
| NEWS 1  |        | Web Page URLs for STN Seminar Schedule - N. America                      |
| NEWS 2  | Dec 17 | The CA Lexicon available in the CAPLUS and CA files                      |
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FILE 'HOME' ENTERED AT 17:41:44 ON 21 SEP 2001

=> file medline emabse biosis caplus cancerlit scisearch toxline

# BONNIE

HPS Trailer Page  
for

## Walk-Up\_Printing

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Printer: cm1\_8e12\_gbelptr

### Summary

| Document    | Pages | Printed | Missed |
|-------------|-------|---------|--------|
| US005677144 | 70    | 70      | 0      |
| US005912183 | 41    | 41      | 0      |
| Total (2)   | 111   | 111     | 0      |

## Freeform Search

Database: US Patents Full-Text Database

17 near3 benjamin

Term:

Display 10 Documents in Display Format: TI

Generate: ☐ Hit List ☒ Hit Count ☐ Image

Search

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Main Menu

Show 8 Numbers

Edit 8 Numbers

## Search History

| <u>DB Name</u> | <u>Query</u>   | <u>Hit Count</u> | <u>Set Name</u> |
|----------------|--|------------------|-----------------|
| USPT           | 17 near3 benjamin  | 7                | <u>L8</u>       |
| USPT           | margolis   | 993              | <u>L7</u>       |
| USPT           | 15 not 14  | 6                | <u>L6</u>       |
| USPT           | shc same (trk or trka)                                   | 11               | <u>L5</u>       |
| USPT           | shc same (egf or endothelial near1 growth near1 factor)  | 15               | <u>L4</u>       |
| USPT           | shc same (her-2 or erbB-2 or cerbB-2 or c-erbB-2 or neu) | 2                | <u>L3</u>       |
| USPT           | apb near5 (domain or recognition)                        | 4                | <u>L2</u>       |
| USPT           | abp near5 (domain or recognition)                        | 2                | <u>L1</u>       |

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File 159:Cancerlit 1975-1999/Nov  
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\*File 159: reloaded, note accession numbers changed.

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File 653:US Patents Fulltext 1980-1989  
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\*File 653: Reassignment data now current through 07/09/99.

Reexamination, extension, expiration, reinstatement updated weekly.

File 654:US PAT.FULL. 1990-1999/DEC 28  
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| Set | Items | Description   |
|-----|-------|---|
| S1  | 15    | APB(5N) (DOMAIN? OR RECOGNITION?)   |
| S2  | 8     | RD (unique items)   |
| S3  | 5224  | SHC   |
| S4  | 281   | S3(5N) (EGF OR ENDOTHELIAL(W) GROWTH(W) FACTOR)                               |
| S5  | 5     | S4(5N) (CANCER OR TUMOR? OR TUMOUR? OR MALIGNAN? OR NEOPLAS?<br>OR CARCINOM?) |
| S6  | 2     | RD (unique items)   |
| S7  | 88    | S3(5N) (HER OR ERBB OR NEU)   |
| S8  | 33    | RD (unique items)   |
| S9  | 116   | S3(5N) (TRK OR TRKA)  |
| S10 | 39    | RD (unique items)   |
| S11 | 48    | E4, E6  |

2/7/3 (Item 2 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1999 BIOSIS. All rts. reserv.

09996798 BIOSIS NO.: 199598451716  
USF binds to the APB-alpha sequence in the promoter of the amyloid  
beta-protein precursor gene.  
AUTHOR: Vostrov Alexander A; Quitschke Wolfgang W; Vidal Frederique;  
Schwarzman Alexander L; Goldgaber Dmitry(a)  
AUTHOR ADDRESS: (a)Dep. Psychiatry Behavioral Sci., State Univ. New York,  
Stony Brook, NY 11794-8101\*\*USA  
JOURNAL: Nucleic Acids Research 23 (14):p2734-2741 1995  
ISSN: 0305-1048  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The **APB-alpha domain** in the amyloid beta-protein  
precursor (APP) promoter contains a nuclear factor binding domain with  
the core recognition sequence TCAGCTGAC. Proteins in nuclear extracts  
from brain and numerous cell lines bind to this domain and it contributes  
approx 10-30% to the basal APP promoter activity. Included in this domain  
is the CANNTG motif, which is recognized by basic helix-loop-helix  
transcription factors. The same motif is also present in the CDEI element  
of the yeast centromere and in the adenovirus major late promoter  
(AdMLP). Here we present evidence based on thermostability, relative  
binding affinity, electrophoretic mobility and antibody recognition that  
the cellular proteins that bind to the APB-alpha and CDEI motifs are USF.  
However, the relative binding affinity for the motifs is different. The  
affinity of USF for AdMLP is approx 20-fold higher than for the APB-alpha  
sequence and 5-fold higher than for the CDEI sequence. Mutational  
analysis suggested that the primary determinant for USF binding affinity  
resides within the octamer CAGCTGAC, which is composed of the E-box  
consensus sequence CANNTG followed by the dinucleotide AC. The human  
homolog of the mouse CDEI binding protein did not bind to either the CDEI  
sequence or APB-alpha.

2/7/4 (Item 3 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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09435834 BIOSIS NO.: 199497444204  
Two nuclear factor binding domains activate expression from the human  
amyloid beta-protein precursor promoter.  
AUTHOR: Quitschke Wolfgang W  
AUTHOR ADDRESS: Dep. Psychiatry Behavioral Sci., State Univ. New York,  
Stony Brook, NY 11794-8101\*\*USA  
JOURNAL: Journal of Biological Chemistry 269 (33):p21229-21233 1994  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Amyloid beta-protein is derived from the amyloid beta-protein  
precursor (APP), and it is a major component of brain amyloid depositions  
in Alzheimer's disease and Down's syndrome. Overexpression of APP may be  
one of several factors contributing to amyloid formation. The APP



promoter was therefore analyzed to determine the mechanism by which APP gene expression is regulated. Cell type-specific expression from the human APP promoter is accomplished with 94 base pairs upstream from the main transcriptional start site. This promoter region contains two nuclear factor binding domains, designated APB-alpha and APB-beta. The contribution of these binding domains to promoter activity was analyzed by transient transfection in HeLa and PC-12 cells. Under standard culture conditions, at least 70-90% of the total activity from the APP promoter can be attributed to binding domain APB-beta. The **recognition domain** for this nuclear factor binding site is defined by the sequence GCCGCTAGGGGT (position -93 to -82). The contribution of binding site APB-alpha to APP promoter activity is considerably lower and represents 10-30% of the total activity. The recognition site for the nuclear factor that binds to APB-alpha is delineated by the sequence GGATCAGCTGAC (position -53 to -42). Elimination of both binding sites causes APP promoter activity in vivo to decline to near background levels.

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02258023 4319466

The zinc finger protein CTCF binds to the **APB** beta domain of the amyloid beta -protein precursor promoter: Evidence for a role in transcriptional activation

Vostrov, A.A.; Quitschke, W.W.

Department of Psychiatry and Behavioral Science, State University of New York, Stony Brook, New York 11794-8101, USA

J. BIOL. CHEM. vol. 272, no. 52, pp. 33353-33359 (1997)

ISSN: 0021-9258

DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

SUBFILE: Biochemistry Abstracts 2: Nucleic Acids; CSA Neurosciences Abstracts

The promoter of the amyloid beta -protein precursor (APP) gene directs high levels of cell type-specific transcription with 94 base pairs 5' to the main transcriptional start site. An essential activator domain in this proximal APP promoter is a nuclear factor binding site designated as **APB** beta . The **recognition domain** for the **APB** beta binding factor is located between position -93 and -82 relative to the main transcriptional start site. The nuclear factor that binds to the **APB** beta site was partially purified by multiple steps of ion exchange and hydroxyapatite chromatography. Based on UV cross-linking results, a protein with an apparent molecular mass of 140 kDa was selected as the putative **APB** beta binding protein. After the final purification step consisting of preparative SDS-polyacrylamide gel electrophoresis, partial peptide sequences were obtained that completely matched the transcriptional factor CTCF. This protein is a known regulator of c-myc and lysozyme gene expression, and it binds to a variety of diverse DNA sequences. The binding of CTCF to the **APB** beta domain was further established by competition with CTCF binding oligonucleotides in mobility shift electrophoresis. The identity was also confirmed by the observation that the **APB** beta binding factor is recognized by antibodies against C- and N-terminal sequences of CTCF. In addition, oligonucleotide competition during in vitro transcription affirmed that CTCF acts as a transcriptional

8/7/13 (Item 13 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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09360728 BIOSIS NO.: 199497369098  
Identification of c-erbB-3 binding sites for phosphatidylinositol 3'-kinase  
and SHC using an EGF receptor/c-erbB-3 chimera.  
AUTHOR: Prigent Sally A; Gullick William J(a)  
AUTHOR ADDRESS: (a)Mol. Oncol. Lab., ICRF Oncol. Group, Hammersmith Hosp.,  
Du Cane Road, London W12 0HS\*\*UK  
JOURNAL: EMBO (European Molecular Biology Organization) Journal 13 (12):p  
2831-2841 1994  
ISSN: 0261-4189  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: c-erbB-3 is a member of the type I (EGF receptor-related) family  
of growth factor receptors for which no ligand has been identified. To  
facilitate ligand stimulation we have constructed a chimeric receptor  
which possesses an activatable kinase and promotes the growth of NIH 3T3  
fibroblasts. In this study we have shown that SHC and  
phosphatidylinositol 3'-kinase bind to the activated EGF  
receptor/c-erbB-3 chimera. Whereas p85 is not phosphorylated to a  
significant extent, SHC appears to be a major substrate for  
phosphorylation on tyrosine. In contrast to EGF receptor and c-erbB-2, we  
were unable to detect binding of activated c-erbB-3 to GRB2. Using  
synthetic peptides corresponding to each of 13 potential phosphorylation  
sites on c-erbB-3, we have shown that tyrosine 1309 is responsible for  
SHC binding. Peptides containing the motif YXXM inhibit p85 association.  
By comparison with recently reported SHC binding sites on Middle T  
antigen and Trk we have identified a SHC binding motif, NPXY.

10/7/16 (Item 16 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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09611615 BIOSIS NO.: 199598066533  
Signaling via the NGF receptor: The **SHC** and CRK proteins associate with **TRK** A in transfected neuronal cells.  
AUTHOR: Torres M; Bogenmann E  
AUTHOR ADDRESS: Dep. Pediatrics, University Southern Carolifornia, Los Angeles, CA 90027\*\*USA  
JOURNAL: Molecular Biology of the Cell 5 (SUPPL.):p265A 1994  
CONFERENCE/MEETING: Thirty-fourth Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 10-14, 1994  
ISSN: 1059-1524  
RECORD TYPE: Citation  
LANGUAGE: English

10/7/17 (Item 17 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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09596507 BIOSIS NO.: 199598051425  
Role of Shc in the activation of Ras in response to epidermal growth factor and nerve growth factor.  
AUTHOR: Basu Tanya; Warne Patricia H; Downward Julian(a)  
AUTHOR ADDRESS: (a)Imperial Cancer Res. Fund, 44 Lincoln's Inn Fields, London WC2A 3PX\*\*UK  
JOURNAL: Oncogene 9 (12):p3483-3491 1994  
ISSN: 0950-9232  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Treatment of the rat pheochromocytoma cell line PC12 with nerve growth factor (NGF) or epidermal growth factor (EGF) is known to result in activation of Ras. In response to EGF treatment, complexes form between Sos, Grb2 and tyrosine phosphorylated Shc and/or EGF receptor. In response to NGF treatment, complexes form between Sos, Grb2 and tyrosine phosphorylated She. While Shc is also found bound to the activated NGF receptor, Trk, no complexes were detectable that contained both Trk and Grb2 or Sos. In streptolysin O permeabilized cells, a tyrosine phosphopeptide, EGFR1068P, which binds to the SH2 domain of Grb2, totally blocks growth factor induced formation of complexes between Grb2 and Shc or EGF receptor, and also blocks activation of nucleotide exchange on Ras. At low concentrations, another tyrosine phosphopeptide, TRKY490P, which binds to the SH2 domain of She, blocks growth factor induced formation of complexes between **Shc** and the EGF receptor or **Trk**, but fails to block activation of nucleotide exchange on Ras. Higher concentrations of **TRK**-Y490P inhibit tyrosine phosphorylation of **Shc** and the formation of Shc complexes with Grb2: this results in strong inhibition of Ras activation by NGF and partial inhibition of Ras activation by EGF. These data demonstrate that the formation of a trimeric complex between tyrosine phosphorylated Shc, Grb2 and Sos is the key event in the activation of Ras in response to NGF. The binding of Sos to tyrosine phosphorylated receptor, via Grb2 may also contribute to Ras activation by EGF but not NGF, while stable complex formation between Shc and receptors is not necessary for Ras activation by either growth factor.

10/7/18 (Item 18 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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09412222 BIOSIS NO.: 199497420592  
P75 nerve growth factor receptor modulates p140-trkA kinase activity, but not ligand internalization, in PC12 cells.  
AUTHOR: Kahle P; Barker P A; Shooter E M; Hertel Cornelia(a)  
AUTHOR ADDRESS: (a)Pharma Div., Preclinical Res., F. Hoffman-La Roche Ltd., CH-4002 Basel\*\*Switzerland  
JOURNAL: Journal of Neuroscience Research 38 (5):p599-606 1994  
ISSN: 0360-4012  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The biological activity of nerve growth factor (NGF) has been shown to be mediated by the p140-trkA receptor tyrosine kinase, while the role of the p75 NGF receptor (p75-NGFR) is still unresolved. Here we have investigated the relative contribution of p140-trkA and p75-NGFR to early consequences of NGF binding: ligand internalization, p140-trkA autophosphorylation, and tyrosine phosphorylation of Shc, phospholipase C-gamma-1(PLC-gamma-1), and extracellular signal-regulated kinases (ERKs). It was found that NGF internalization was neither prevented by blocking p140-trkA activity using the protein kinase inhibitors methylthioadenosine, staurosporine, and K-252a, nor by inhibiting NGF binding to p75-NGFR with antibodies. However, when NGF binding to p140-trkA was reduced by the use of a synthetic peptide corresponding to amino acids 36-53 of human p140-trkA, internalization of NGF was decreased. Thus, at least in PC12 cells, internalization appears to require binding of NGF to p140-trkA, but occurs irrespective of p140-trkA kinase activity and ligand occupancy of p75-NGFR. The NGF triple mutant Lys-32/Lys-34/Glu-35 to Ala, which has been demonstrated to bind to p140-trkA, but not to p75-NGFR, induced tyrosine phosphorylation more rapidly than wild-type NGF. Likewise, NGF-induced tyrosine phosphorylation was accelerated when NGF binding to p75-NGFR was prevented with REX-IgG. These findings indicate that NGF binding by p75-NGFR may modulate NGF-induced p14-trkA kinase activity.

10/7/19 (Item 19 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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AUTHOR: Prigent Sally A; Gullick William J(a)  
AUTHOR ADDRESS: (a)Mol. Oncol. Lab., ICRF Oncol. Group, Hammersmith Hosp., Du Cane Road, London W12 0HS\*\*UK  
JOURNAL: EMBO (European Molecular Biology Organization) Journal 13 (12):p 2831-2841 1994  
ISSN: 0261-4189  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: c-erbB-3 is a member of the type I (EGF receptor-related) family of growth factor receptors for which no ligand has been identified. To facilitate ligand stimulation we have constructed a chimeric receptor which possesses an activatable kinase and promotes the growth of NIH 3T3 fibroblasts. In this study we have shown that SHC and phosphatidylinositol 3'-kinase bind to the activated EGF

receptor/c-erbB-3 chimera. Whereas p85 is not phosphorylated to a significant extent, SHC appears to be a major substrate for tyrosine phosphorylation on tyrosine. In contrast to EGF receptor and c-erbB-2, we were unable to detect binding of activated c-erbB-3 to GRB2. Using synthetic peptides corresponding to each of 13 potential phosphorylation sites on c-erbB-3, we have shown that tyrosine 1309 is responsible for SHC binding. Peptides containing the motif YXXM inhibit p85 association. By comparison with recently reported SHC binding sites on Middle T antigen and **Trk** we have identified a **SHC** binding motif, NPXY.

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The oncogenic versions of the Ret and **Trk** tyrosine kinases bind **Shc** and Grb2 adaptor proteins.

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JOURNAL: Oncogene 9 (6):p1661-1668 1994

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ABSTRACT: Proto-TRK and proto-RET genes encode receptor type tyrosine kinases. Oncogenic rearrangements of both proto-oncogenes have been detected with a significant frequency in human papillary thyroid carcinomas. Chimeric Ret and Trk oncoproteins, encoded by different rearrangements of proto-TRK and proto-RET genes, display a constitutive phosphorylation on tyrosine. Moreover, it has been shown that phosphorylated tyrosine receptors, activated by their ligands, form multiprotein complexes responsible for transducing mitogenic or differentiation signals. We have therefore begun to analyse in this study the signal transduction pathways triggered by different Ret and Trk oncoproteins. We have shown that the SH2 domain of the adaptor protein Shc coimmunoprecipitates with all the Ret and Trk oncoproteins as well as with NGF-activated proto-Trk receptor. Tyrosine phosphorylation of Trk proteins both normal and oncogenic is necessary for their binding to Shc. In addition, in cells containing either Ret or **Trk** oncoproteins, **Shc** proteins are constitutively phosphorylated on tyrosine and bound to Grb2. Only in in vitro experiments were Ret and Trk oncoproteins shown to bind the SH2 region of Grb2. Finally, when proto-**Trk** product is stimulated by NGF, **Shc** phosphorylation and association with Grb2 are induced. In conclusion, we have shown that Ret and Trk oncoproteins can form multiprotein complexes, however, the functional meaning of the described interactions has to be elucidated.

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Neuronal differentiation signals are controlled by nerve growth factor receptor/**Trk** binding sites for **SHC** and PLC-gamma.

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ABSTRACT: Differentiation and survival of neuronal cell types requires the action of neurotrophic polypeptides such as nerve growth factor (NGF). In the central and peripheral nervous system and the pheochromocytoma cell model PC12, NGF exerts its effects through the activation of the signalling capacity of Trk, a receptor tyrosine kinase (RTK) which upon interaction with NGF becomes phosphorylated on tyrosines and thereby acquires the potential to interact with signal-transducing proteins such as phospholipase C-gamma (PLC-gamma), phosphatidylinositol-3'-kinase (PI3'-K) and SHC. Mutagenesis of the specific binding sites for these src homology 2 (SH2) domain-containing substrates within the Trk cytoplasmic domain suggests a non-essential function of PI3'-K and reveals a major role for the signal controlled by the SHC binding site at tyrosine 490 and a co-operative function of the PLC-gamma-mediated pathway for neuronal differentiation of PC12 cells.

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Identification of **Trk** binding sites for **SHC** and phosphatidylinositol 3'-kinase and formation of a multimeric signaling complex.

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JOURNAL: Journal of Biological Chemistry 268 (31):p22963-22966 1993

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ABSTRACT: Phosphotyrosine-containing synthetic peptides were used to identify the binding sites for cellular polypeptides involved in nerve growth factor receptor/Trk-mediated signal transduction. In vitro association of SHC and the p85 subunit of phosphatidylinositol 3'-kinase with the Trk tyrosine kinase was prevented only by phosphorylated Y-490- and Y-751-containing peptides, respectively. In spite of the close proximity of the p85 binding site to that of phospholipase C-gamma (Y-785), both target proteins are able to interact with the same receptor molecule simultaneously.

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Trk receptors use redundant signal transduction pathways involving SHC and PLC-gammal to mediate NGF responses

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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In response to NGF, the Trk receptor tyrosine kinase forms a complex with SHC, a protein that couples receptor tyrosine kinases to p21(ras). Complex formation between **Trk** and **SHC**, **SHC** tyrosine phosphorylation, and association of SHC with Grb2 were mediated by autophosphorylation at V490 in Trk (NPQYFSD). To determine the role of **SHC** and other **Trk** substrates in NGF signaling, Trk receptors with mutations in Y490 and Y785 (the PLC-gammal association site) were introduced into PC12nnr5 cells. NGF treatment of PC12nnr5 cells expressing Trk with mutations in either substrate-binding site resulted in normal neurite outgrowth and Erk1 activity and tyrosine phosphorylation. However, PC12nnr5 cells expressing Trk with mutations at both sites failed to stably extend neurites and efficiently induce Erk1 activity and tyrosine phosphorylation in response to NGF. We postulate that Trk receptors can activate Erk1 by either SHC- or PLC-gammal-dependent signaling pathways. These results suggest a model whereby Trk receptors utilize at least



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P75 nerve growth factor receptor modulates p140 super(trkA) kinase activity, but not ligand internalization, in PC12 cells  
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The biological activity of nerve growth factor (NGF) has been shown to be mediated by the p140 super(trkA) receptor tyrosine kinase, while the role of the p75 NGF receptor (p75 super(NGFR)) is still unresolved. Here we have investigated the relative contribution of p140 super(trkA) and p75 super(NGFR) to early consequences of NGF binding: ligand internalization, p140 super(trkA) autophosphorylation, and tyrosine phosphorylation of Shc, phospholipase C sub( gamma -1) (PLC sub( gamma -1)), and extracellular signal-regulated kinases (ERKs). It was found that NGF internalization was neither prevented by blocking p140 super(trkA) activity using the protein kinase inhibitors methylthioadenosine, staurosporine, and K-252a, nor by inhibiting NGF binding to p75 super(NGFR) with antibodies. The findings indicate that NGF binding by p75 super(NGFR) may modulate NGF-induced p140 super(trkA) kinase activity.